

Integrative computational modeling of calcium handling and cardiac arrhythmias

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Summary

$$\frac{dX}{dt} = \alpha_x (1 - X) - \beta_x X$$

$$\delta I_{Ca,L}^{s,m} = \theta I_{Ca,L} \cdot \frac{X_{Ca,L} \cdot y_{S_{Ca,L}}^{s,m} \cdot \delta_{Ca,L}^{s,m}}{y_{Ca,L} \cdot X_{S_{Ca,L}}^{s,m} \cdot \theta_{Ca,L}}$$

$$\cdot \frac{X_{Ca,L} \cdot y_{S_{Ca,L}}^{s,m} \cdot \delta_{Ca,L}^{s,m}}{y_{Ca,L} \cdot X_{S_{Ca,L}}^{s,m} \cdot \theta_{Ca,L}}$$

$$I_{Ca,L}^{s,m} = \bar{I}_{Ca,L}^{s,m} \cdot (O_{Ca,L}^{s,m} + O_{S_{Ca,L}}^{s,m})$$

$$\cdot \frac{\frac{V_m \cdot F^2}{R \cdot T} \cdot \frac{y_{Ca,i} \cdot [Ca^{2+}]_{obs}^{s,m} \cdot \exp\left(z_{Ca} \cdot V_m \cdot \frac{F}{R \cdot T}\right) - y_{Ca,o} \cdot [Ca^{2+}]_o}{\exp\left(z_{Ca} \cdot V_m \cdot \frac{F}{R \cdot T}\right) - 1} \cdot \frac{\exp(0.052 \cdot (V_m + 13))}{1 + \exp(0.132 \cdot (V_m + 13))}$$

$$\frac{dV}{dt} = \frac{I_{stim} - (I_K + I_{Na} + I_{leak})}{C_m}$$

Summary

Cardiomyocyte calcium handling is a major determinant of excitation-contraction coupling. Alterations in one or more calcium-handling proteins may induce arrhythmias through the formation of ectopic activity, direct and indirect ion-channel regulation, and structural remodeling. Due to the complex and tight interactions between calcium and other molecules within a cardiomyocyte, it remains experimentally challenging to study the exact contributions of calcium-handling abnormalities to arrhythmogenesis. Multiscale computational studies performed in close collaboration with laboratory experiments create new opportunities to unravel the mechanisms of arrhythmogenesis. This thesis describes the roles of integrative computational modeling in unraveling the arrhythmogenic consequences of calcium-handling abnormalities.

In **Chapter 2**, we reviewed the complex mechanisms and proarrhythmic consequences of calcium-dependent ion-channel regulation, SCAEs, post-translational calcium-signaling pathways, and long-term transcriptional regulation of calcium handling. We also discussed potential advantages of combined *in vitro* and *in silico* studies to address such complexities.

In **Chapter 3**, we employed the perfect control and observability provided by computer models to elucidate the subcellular determinants of cardiomyocyte calcium handling. Our findings highlighted the importance of subcellular RyR2 and LTCC distributions in the genesis of SCAEs and DADs, which are well-known triggers of cardiac arrhythmias. Importantly, whole-cell calcium handling properties are determined by non-linear interactions between heterogeneities in the expression and phosphorylation of both LTCC and RyR2, highlighting the need for detailed immunocytochemistry and functional studies to explain differences in whole-cell calcium handling between conditions.

Chapter 4 illustrated the application of the spatial calcium-handling model from **Chapter 3** to support the notion that post-operative inflammation acting on a pre-existing arrhythmogenic substrate may elicit SCAEs and DADs that could initiate POAF.

Meanwhile, in **Chapter 5**, our multiscale *in silico* study demonstrated that calcium-dependent regulation of atrial ionic currents alters human atrial electrophysiology at the cellular and tissue level. It has protective effects in non-diseased atrium by stabilizing the membrane potential, lowering DAD amplitude and preventing TA. However, in the presence of cAF-related remodeling, calcium-dependent ion-channel regulation has proarrhythmic APD-shortening and RMP-hyperpolarizing effects, stabilizing reentrant waves. We identified I_{K1} and I_{SK} as the major ionic contributing factors.

Chapter 6 of this thesis showed how our multiscale *in-silico* study provides new insights into the acute effects of ethanol on cardiac electrophysiology and arrhythmogenesis, demonstrating that ethanol has concentration-dependent

Summary

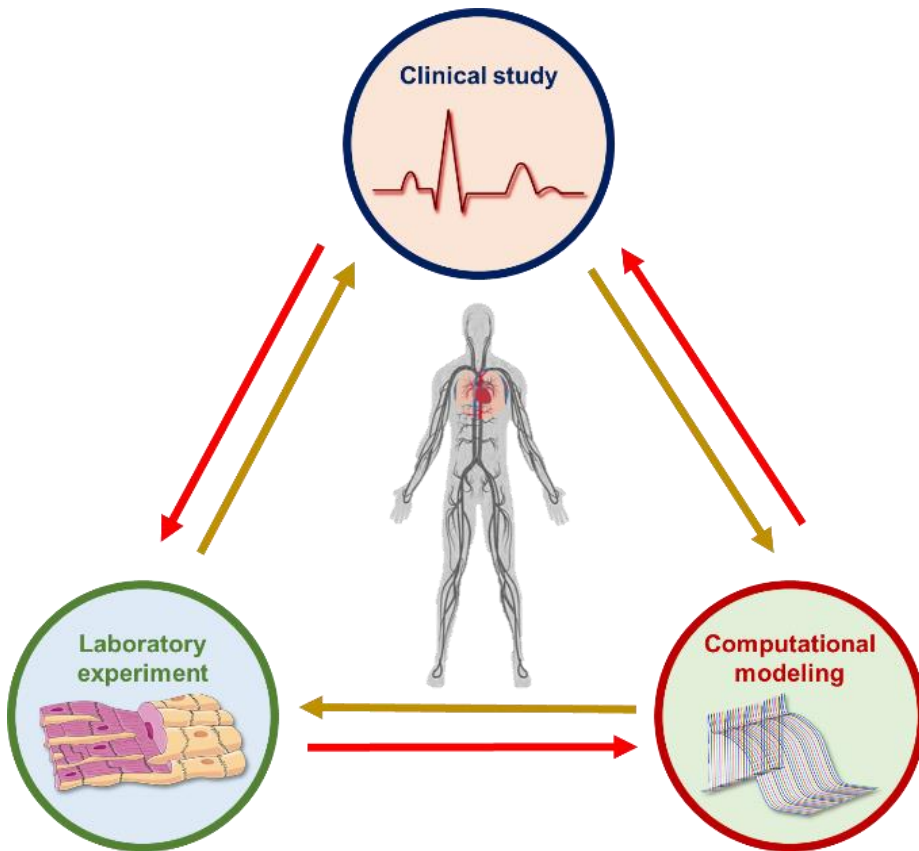
electrophysiological effects that differ between atria and ventricles, and in the absence or presence of disease-related remodeling. Low concentrations of ethanol had antiarrhythmic effects in the atria, whereas high concentrations promoted reentrant arrhythmias. In this chapter, we also showed that the exact proarrhythmic risk depends on ethanol-induced gap-junction remodeling and the degree, type and pattern of disease-associated structural remodeling, highlighting the need for personalized multiscale computational modeling to better predict the consequences of ethanol on cardiac electrophysiology in humans.

Chapter 7 introduced MANTA, a powerful, freely available tool to reproduce a wide range of AAD characteristics including species-, rate-, and disease-dependent effects. MANTA enables analyses of the underlying ionic mechanisms as well as investigations of novel AADs with specific affinities for one or more targets. MANTA can facilitate a better understanding of the complex effects of AADs on cellular electrophysiology under a wide range of conditions, which may provide educational and/or clinically-relevant information on the safety and efficacy of AAD treatment.

Chapter 8 demonstrated the synergistic APD-prolonging effect of CQ and AZM, which potentially increases the proarrhythmic risk, although the severity of the electrophysiological effects depends on the baseline repolarization reserve. Additionally, we showed that transient activation of the sympathetic nervous system may prevent CQ- and AZM-induced proarrhythmia by reducing their APD-prolonging effect, highlighting the importance of preserving β -adrenergic response in the presence of such proarrhythmic medications, and the potential significance of heart-rate and autonomic-status monitoring in conditions such as COVID-19.

Finally, **Chapter 9** wrapped up this thesis with an *aide-mémoire* that calcium-handling abnormalities have multiscale implications that may promote cardiac arrhythmias. Integrative computational modeling enables investigations into the arrhythmogenic mechanisms and consequences of alterations in cardiac calcium handling, although some challenges remain. Future arrhythmia research would benefit from organ-level, and, more importantly, integrative personalized / patient-specific modeling approaches, which will certainly improve the accuracy and clinical applicability of computational models.

In the end, *in silico* models will always be *in silico*. Therefore, synergistic interactions with clinical studies and biological experiments are an absolute prerequisite to address unmet needs of current arrhythmia research.



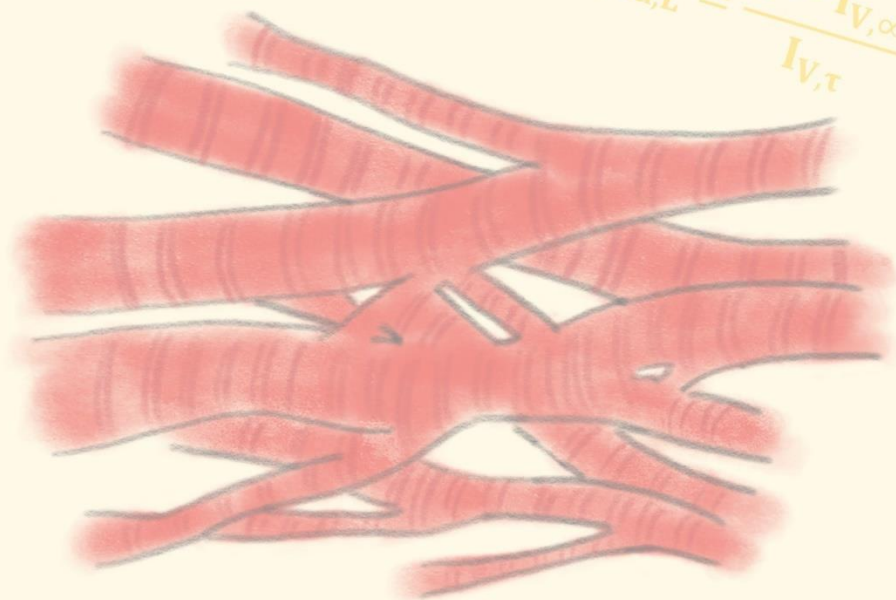
Summary figure: Three pillars of cardiovascular research. In the future, an integrative synergy between clinical studies, laboratory experiments and computational modeling would be beneficial in addressing the knowledge gaps and unmet needs of current arrhythmia research.



$$\frac{dV_m}{dt} = -\frac{1}{C_m} * I$$

$$y_{Ca,L} = \frac{1 - I_{V,\infty}}{I_{V,\tau}}$$

$$x_{Ca,L} = \frac{I_{V,\infty}}{I_{V,\tau}}$$



$$\frac{dV_i}{dt} = -\frac{1}{C} (I_{ion,i} + I_{stim,i} + I_{diff,i})$$

$$\delta I_{Ca,L}^{s,m} =$$

$$\bar{I}_{Ca,L}^{s,m} = P_{Ca,L} \cdot (z$$

$$ACT_{\tau} = 0.59$$

